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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,278	11/05/2001	Sydney David Finkelstein	FINKEL-1 CONT II	2727

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Ansel M. Schwartz
Suite 304
201 N. Craig Street
Pittsburgh, PA 15213

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/15/2003

2

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,278	FINKELSTEIN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1-17 are pending.

Priority

2. This application claims priority to 08/667,493, filed June 24, 1996 and 08/311,553, filed September 23, 1994.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Specification

3. On page 22, line 7, the specification recites "cite?". It is unclear whether there is a cite missing from the disclosure or whether this recitation is in error. Applicant is reminded that no new matter may be added.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 4 lacks proper antecedent basis over the recitation "the cutting step". Claim 1, from which Clam 4 depends, does not set forth a cutting step. Therefore, "the cutting step" lacks proper antecedent basis.

B) Claim 5 is indefinite because it is unclear whether "the specimen is a filter" or whether the specimen in on a filter. Claim 1, from which Claim 5 depends requires a biological specimen. A filter is not a biological specimen. Therefore, it is unclear whether the claim is referring to a distinct specimen or whether the claim was intended to encompass a specimen on a filter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 6-7, 10-12, 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Pretlow et al. (J. of Natl. Cancer Institute, Vol. 85, No. 24, pages 2004-2007, December 1993).

Pretlow et al. (herein referred to as Pretlow) teaches a method of detecting K-ras mutation in putative preneoplastic lesions in human colon. Pretlow teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Pretlow teaches obtaining human colon specimens (limitations of Claim 2). Strips of mucosa were fixed, stained and aberrant crypt foci were identified (limitations of Claim 1a, b, 3)(page 2005, col 1). Aberrant crypt focus were identified and microdissected (limitations of Claim 1c, d)(page 2005, col. 1). The samples were suspended in Tris buffer, EDTA, Tween and proteinase K (limitations of Claim 1e, 6-7)(page 2005, col. 1-2). PCR amplification of the DNA region containing codon 12 of K-ras was performed (limitations of Claim 1f g, 10-12, 15)(page 2005, col. 2-3). The PCR products were hybridized with a radiolabeled probe and autoradiographed (page 2005, col. 3). Since Pretlow teaches every limitation of the instant claims, Pretlow anticipates the claimed invention.

6. Claims 1-3, 6-7, 10-12, 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Teramoto et al (Acta Med. Okayama, Vol. 48, No. 4, pages 189-193, 1994).

Teramoto et al. (herein referred to as Teramoto) teaches application of PCR to the microscopically identified cells on the sides. Teramoto teaches a method of placing

a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically Teramoto teaches observing target cells on the mounted specimens microscopically (limitations of Claim 1a, b)(page 190, col. 1). The location of the cells were recorded by a microscanner which made it easy to localize the target cells. The cells were picked up using a micromanipulator and placed on a coverglass (limitations of Claim 1c, d, 2, 3) (page 190, col. 1). Since single cells may be obtained, the "piece" which is separated is less than .5 cm2 and the micromanipulator may be interpreted as "slicing" the section (see Figures 1 and 2). The picked cells were transferred into PCR tubes and were processed prior to subjecting to gene amplification of HTLV-I (limitations of Claim 1e, 4-7, 10, 15)(page 190, col. 1). The transferred cells were digested with 1mg/ml Proteinase K at 37 degrees C in 30 ul of digestion buffer; 10 mM Tris-HCl, 0.45% NP-40 and 0.45% Tween-20 (limitations of Claim 6-7). The amplified DNA was analyzed with ethidium bromide staining of the gel and Southern blot hybridization (limitations of Claim 1f, 10-12)(page 190, col. 1). Gel electrophoresis may be interpreted as a separating step which is capable of separating fragments which are less than 100 bases from those which are greater than 100 base pairs in length. Teramoto teaches tissues such as smears of peripheral blood and tissues resected from the stomach were analyzed (page 190, col. 1)(limitations of claims 2-3).

Therefore, since Teramoto teaches every limitation of the claimed invention, Teramoto anticipates the instant claims.

7. Claims 1-2, 4, 6-7, 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992).

Shibata et al. (herein referred to as Shibata) teaches a method of specific genetic analysis of microscopic tissue after selective ultraviolet radiation Fraction and the polymerase chain reaction. Shibata teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Shibata teaches using stained sections of tissues which are approximately 0.1 cm thick (limitations of Claim 1 a b, 2). Under the microscope, cells were selected and then dotted by hand with a felt-tip pen (limitations of Claim 1 c). The slide was separated and placed into microfuge tubes (limitations of Claim 4). For studies of p53 gene expression/mutations only 3x3 mm areas surrounding the dotted areas were placed in microfuge tubes (i.e. a piece of the sample is separated, having a size essentially .5cm or less, from the specimen with the target part of the piece)(limitations of Claim 1d). DNA was then extracted and the boiled (limitations of Claim 1e, 6). The extraction solution comprises a lysis buffer of 100 mmol/l Tris-HCL, 2 mmol/l ethylene

diamine tetraacetic acid and proteinase K (limitations of Claim 7). Upon extraction, PCR assays were used to detect several targets (limitations of Claim 1f). PCR products were analyzed with two specific oligomers to distinguish between the two alleles (limitations of Claim 10, 11, 12). Tissue sections were examined for the loss of herterozygosity of p53 and the technique was demonstrated to be effective in detecting LOH in the small number of target cells selected as being neoplastic in contrast to cells that were selected as being non-neoplastic (limitations of Claim 1g, 15). Therefore, since Shibata teaches every limitation of the claims, Shibata anticipates the claimed invention.

8. Claims 1-2, 4, 6-8, 10-12, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Meltzer et al (PNAS, Vol. 88, pages 4976-4980, June 1991).

Meltzer et al. (herein referred to as Meltzer) teaches a method of detecting LOH using PCR. Meltzer modified the PCR reaction to enable detection of LOH using small quantities of DNA obtained from microdissected frozen biopsies or archival paraffin sections (page 4976, col. 2). Meltzer teaches a genotyping method comprising obtaining a specimen of cells containing DNA and placing under a microscope, inspecting the cells to determine target cells, choosing target ells based on morphological features characteristic of a disease and separating the target cells (page 4976, col. 2, para 2) by teaching that cell samples were obtained from patients with esophageal cancer frozen in liquid nitrogen, embedded in paraffin and microdissected by placing the sample under the microscope and observing morphological differences

between the tumor areas and normal cells (limitations of Claims 1a, b, c, d, 2, 4). Meltzer then teaches that the tumor cells were microdissected to separate them from adjacent normal cells to achieve an enrichment of about 70% or greater. Meltzer then places the separated piece into a container, centrifuging to make a pellet and withdrawing supernatant to obtain DNA (page 4976, col. 2, para 3) by teaching that the separated tissue was placed into a container, ground into a powder, incubated in a container in a lysis solution, treated with phenol/chloroform and ethanol which involved centrifugation to make a pellet and removal of supernatant containing DNA (limitations of Claim 1e, 6-8). Meltzer then teaches that the method amplifies the isolated DNA by PCR and detects a mutation associated with the cancer, i.e. the loss of herterozygosity in the p53 region of chromosome 17 (page 4977, col. 1 and page 4978, col. 2)(limitations of Claim 1f g, 10, 11, 12, 15). Therefore, since Meltzer teaches every limitation recited in the claims, Meltzer anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2, 4, 6-7, 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuppers et al. (EMBO J. Vol. 12, No. 13, pages 4955-4967, 1993) in view of Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992).

Kuppers et al. (herein referred to as Kuppers) teaches a method wherein section derived from human lymph nodes were stained and single cells were obtained from various histologically distinct areas of the germinal center. Nucleic acids from individual cells were amplified in a semi-nested PCR approach using V gene specific primers and amplification products were identified after separation on an ethidium bromide agarose stained gel. Kuppers teaches that by direct sequence of PCR products somatic mutations could be clearly identified in V region genes.

Kuppers does not teach in his example, identifying cells based on morphological criteria based on a disease, such as cancer, or the detection of a DNA sequence which is associated with the development of progression of the disease.

However, Shibata et al. (herein referred to as Shibata) teaches a method of specific genetic analysis of microscopic tissue after selective ultraviolet radiation fraction and the polymerase chain reaction. Shibeta teaches a method in which cells associated

with a specific pathology are chose or targed and cut away from the remainder of the tissue section for the purpose of detection of a sequence particularly associated with a disease. Shibata teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Shibata teaches using stained sections of tissues which are approximately 0.1 cm thick (limitations of Claim 1 a b, 2). Under the microscope, cells were selected and then dotted by hand with a felt-tip pen (limitations of Claim 1 c). The slide was separated and placed into microfuge tubes (limitations of Claim 4). For studies of p53 gene expression/mutations only 3x3 mm areas surrounding the dotted areas were placed in microfuge tubes (i.e. a piece of the sample is separated, having a size essentially .5cm or less, from the specimen with the target part of the piece)(limitations of Claim 1d). DNA was then extracted and the boiled (limitations of Claim 1e, 6). The extraction solution comprises a lysis buffer of 100 mmol/l Tris-HCL, 2 mmol/l ethylene diamine tetraacetic acid and proteinase K (limitations of Claim 7). Upon extraction, PCR assays were used to detect several targets (limitations of Claim 1f). PCR products were analyzed with two specific oligomers to distinguish between the two alleles (limitations of Claim 10, 11, 12). Tissue sections were examined for the loss of herterozygosity of p53 and the technique was demonstrated to be effective in detecting LOH in the small number of target cells

selected as being neoplastic in contrast to cells that were selected as being non-neoplastic (limitations of Claim 1g, 15).

There, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the method of Kuppers in a method of genotyping given the suggestion of Shibeta of the desirability of detecting sequences in a restricted area of a tissue sample, for example, specifically in cells associated with a pathological state. The method of Shibata allows specific and sensitive molecular genetic analysis of small numbers of cells histologically identified and selected under the microscope (abstract). One of ordinary skill in the art would have obtained a reasonable expectation that the method of Kuppers could be employed successfully in methods of screening as described by Shibeta.

11. Claims 1-12, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pretlow et al. (J. of Natl. Cancer Institute, Vol. 85, No. 24, pages 2004-2007, December 1993).or Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992) or Teramoto et al (Acta Med. Okayama, Vol. 48, No. 4, pages 189-193, 1994) in view of Innis et al. (PCR Protocols, "Optimization of PCRs", pages 3-12, 153-158, 348-355, 1990).

Pretlow et al. (herein referred to as Pretlow) teaches a method of detecting K-ras mutation in putative preneoplastic lesions in human colon. Pretlow teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the

biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Pretlow teaches obtaining human colon specimens (limitations of Claim 2). Strips of mucosa were fixed, stained and aberrant crypt foci were identified (limitations of Claim 1a, b, 3)(page 2005, col 1). Aberrant crypt focus were identified and microdissected (limitations of Claim 1c, d)(page 2005, col. 1). The samples were suspended in Tris buffer, EDTA, Tween and proteinase K (limitations of Claim 1e, 6-7)(page 2005, col. 1-2). PCR amplification of the DNA region containing codon 12 of K-ras was performed (limitations of Claim 1f g, 10-12, 15)(page 2005, col. 2-3). The PCR products were hybridized with a radiolabeled probe and autoradiographed (page 2005, col. 3).

Shibata et al. (herein referred to as Shibata) teaches a method of specific genetic analysis of microscopic tissue after selective ultraviolet radiation Fraction and the polymerase chain reaction. Shibata teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically, Shibata teaches using stained sections of tissues which are approximately 0.1 cm thick (limitations of Claim 1 a b, 2). Under the microscope, cells were selected and then dotted by hand with a felt-tip pen (limitations of Claim 1 c). The slide was separated and placed into microfuge tubes (limitations of Claim 4). For studies of p53

gene expression/mutations only 3x3 mm areas surrounding the dotted areas were placed in microfuge tubes (i.e. a piece of the sample is separated, having a size essentially .5cm or less, from the specimen with the target part of the piece)(limitations of Claim 1d). DNA was then extracted and the boiled (limitations of Claim 1e, 6). The extraction solution comprises a lysis buffer of 100 mmol/l Tris-HCL, 2 mmol/l ethylene diamine tetraacetic acid and proteinase K (limitations of Claim 7). Upon extraction, PCR assays were used to detect several targets (limitations of Claim 1f). PCR products were analyzed with two specific oligomers to distinguish between the two alleles (limitations of Claim 10, 11, 12). Tissue sections were examined for the loss of herterozygosity of p53 and the technique was demonstrated to be effective in detecting LOH in the small number of target cells selected as being neoplastic in contrast to cells that were selected as being non-neoplastic (limitations of Claim 1g, 15).

Teramoto et al. (herein referred to as Teramoto) teaches application of PCR to the microscopically identified cells on the sides. Teramoto teaches a method of placing a biological specimen having DNA of a patient under a microscope; inspecting the biological specimen microscopically; choosing a microscope sized target on the biological specimen based on its histopathologic characteristics; separating the target from the specimen; obtaining DNA; amplifying DNA and detecting mutations in the DNA. Specifically Teramoto teaches observing target cells on the mounted specimens microscopically (limitations of Claim 1a, b)(page 190, col. 1). The location of the cells were recorded by a microscanner which made it easy to localize the target cells. The cells were picked up using a micromanipulator and placed on a coverglass (limitations

of Claim 1c, d, 2, 3) (page 190, col. 1). Since single cells may be obtained, the "piece" which is separated is less than .5 cm2 and the micromanipulator may be interpreted as "slicing" the section (see Figures 1 and 2). The picked cells were transferred into PCR tubes and were processed prior to subjecting to gene amplification of HTLV-I (limitations of Claim 1e, 4-7, 10, 15)(page 190, col. 1). The transferred cells were digested with 1mg/ml Proteinase K at 37 degrees C in 30 ul of digestion buffer; 10 mM Tris-HCl, 0.45% NP-40 and 0.45% Tween-20 (limitations of Claim 6-7). The amplified DNA was analyzed with ethidium bromide staining of the gel and Southern blot hybridization (limitations of Claim 1f, 10-12)(page 190, col. 1). Gel electrophoresis may be interpreted as a separating step which is capable of separating fragments which are less than 100 bases from those which are greater than 100 base pairs in length. Teramoto teaches tissues such as smears of peripheral blood and tissues resected from the stomach were analyzed (page 190, col. 1)(limitations of claims 2-3).

Pretlow, nor Shibata nor Teramoto specifically teaches that the specimen may be obtained from a filter (limitations of Claim 5), or the DNA may be extracted with an additional step of phenol-chloroform extraction (limitations of Claim 8) or PCR cycling temperatures may be performed at temperatures no greater than 99C and extension temperatures are around 55C.

However, Innis et al. (herein referred to as Innis) teaches the conventionality of phenol-chloroform extractions in DNA extraction protocols for use in PCR methods (pages 157, 353). Innis teaches that the inhibitory effects of certain fixatives can be overcome by further purification with phenol-chloroform extraction of the tissue extracts

(page 157, para 3). Additionally, Innis teaches PCR methods wherein the heating step may be from 94-97 C (i.e. not greater than 99C) and a single annealing and extension step whose temperature may be from 55-75C (page 7, para 3).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the DNA extraction methods and detection methods of Pretlow, Shibeta or Teramoto in view of the teachings of Innis given that is it was well known that phenol-chloroform extraction would remove proteins and lipids from a sample and allow one to further purify the DNA. Although the references do not specifically teach that the tissue sample may be obtained from a filter, it would have been prima facie obvious to obtain a cellular sample from any of the conventional means used to obtain clinical samples (limitations of Claim 5). Claims 16-17 recite specific steps of amplification with each cycle heating to no greater than 99 C and then back to about 55C in 5 minutes. Innis teaches PCR methods wherein the heating step may be from 94-97 C (i.e. not greater than 99C) and a single annealing and extension step whose temperature may be from 55-75C (page 7, para 3). Therefore, it would have been prima facie obvious to one of ordinary skill in the art absent any showing of unexpected results to perform PCR cycles using a cycling reaction no greater than 99C and an extension step at 55C (for example) given the teachings of Innis of means to optimize PCR reaction conditions.

12. Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pretlow et al. (J. of Natl. Cancer Institute, Vol. 85, No. 24, pages 2004-2007, December

1993).or Shibata et al. (Am. J. of Pathology, Vol. 121, No. 3, pages 539-543, September 1992) or Teramoto et al (Acta Med. Okayama, Vol. 48, No. 4, pages 189-193, 1994). in view of Innis et al. (PCR Protocols, "Optimization of PCRs", pages 3-12, 153-158, 348-355, 1990) as applied to Claims 1-12, 15-17 above, and further in view of Vogelstein (US Pat. 5,380,645, filed March 1989) and Camble (US Pat. 5,320,840, June 1994).

Neither Pretlow nor Shibata nor Teramoto nor Innis specifically teach the step of using the method in developing a treatment regime and as a means of identifying a source in a patient with cancer.

However, Vogelstein teaches a generalized method for assessing the progression of colorectal cancer wherein DNA is isolated from paraffin sections of neoplastic and nonneoplastic tissues, the extraction of DNA by lysis buffer followed by phenol-chloroform extraction and analysis by PCR. DNA from patient samples is then compared to DNA from nonneoplastic tissues to determine an indicator factor useful for the prognosis of cancer (Figure 2, col. 5, lines 20-27).

Camble further teaches pharmaceutical compositions for use in the treatment of cancer.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used the methods of Pretlwo or Shibata or Teramoto in view of Innis to apply the general methods of screening and prognosis and treatments as taught by Vogelstein and Camble given the teachings of Shibata that the methods was well suited to screening applications. The ordinary artisan would have

been well motivated to use such a screening methods as an aid to develop a treatment method and the broad teachings of the references are commensurate to the teachings of the specification in this regard.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-2 of U.S. Patent No. 6,340,563, January 22, 2002.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 1-17 of the instant application is generic to all that is recited in Claim 1-2 of U.S. Patent No. 6,340,563. That is, Claim 1-2 of 6,340,563 falls entirely within the scope of Claim 1-2, or in other words, Claim 1-17 is anticipated by Claims 1-2 of 6,340,563. Here, claim 1-2 of U.S. Patent No. 6,340,563 recites a method of topographic genotyping consisting of placing a fixative treated tissue specimen of intact cells having DNA of a patient under a microscope; inspecting the fixative treated tissue specimen with the microscope for determination of cellular targets for genetic analysis; choosing a target on the fixative treated tissue specimen based on specific morphological criteria in turn reflecting specific disease related cellular alterations; separating a piece from said chosen target; placing the piece directly into a containing a lysis buffer; performing a single centrifugation on the container; withdrawing supernatant from the pellet in the container; amplifying the DNA sequences directly and detecting mutations in the DNA sequence. The instant claims are broader and encompass each limitation of the patent.

Conclusion

14. No claims allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
January 6, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600